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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/010,802 | 11/09/2001 | Anne Chew | MWH-0002US2 | 7301 |

25106 7590 01/22/2004

GENAISSANCE PHARMACEUTICALS
5 SCIENCE PARK
NEW HAVEN, CT 06511

| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/010,802 | CHEW ET AL. | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25-30* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

1. This office action is written in response to applicant's paper dated 11/14/2003. Claim 30 was added. Claims 26-30 are examined herein. Claim 25 is withdrawn from prosecution. Applicant's remarks have been considered but are not fully persuasive for the reasons that follow. Any rejection not reiterated is withdrawn. **This action is Final.**

### *Claim Rejections - 35 USC § 101 and 112*

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26-30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

5. This rejection is reiterated for claims 26-29 and applied to newly added claim 30. Applicant's remarks are addressed at the end of the office action.

The claims are drawn to methods for predicting a haplotype pair of an individual for the Interleukin 4 Receptor Alpha gene (IL4Rα). The specification does not appear to contain a clear assertion of a utility for the claimed methods, other than the fact that the claimed methods can in fact be used to predict which haplotype pair is present in an individual's genome.

The specification teaches a set of polymorphic sites within the IL4Rα gene that were identified by sequencing portions of the IL4Rα from two reference populations (referred to in the

examples as Index Repository IA (example 1a) and another population of 70 human individuals (example 1b). The positions of the polymorphic sites within a reference sequence are given in Table 3, and illustrated in Figure 1. In example 2, Table 4, the specification provides a sampling of different genotypes containing the polymorphisms that were observed in the reference population, specifically teaching haplotype pairs that were determined using a "derivation protocol." Table 4 contains a listing of haplotype pairs observed in the reference populations for 39 polymorphic sites, but Table 4 also contains some blanks where particular alleles are not identified. The specification teaches that these can typically "be inferred based on linkage disequilibrium and/or Mendelian inheritance." Example 2 teaches that the haplotype pairs were estimated from the unphased genotypes using an extension of Clark's algorithm. Thus, the haplotype pairs presented in Table 4 are not themselves empirically observed haplotype pairs but are an estimation that were deconvulated based on unphased genotypes.

Turning to the method of the claimed invention, the specification asserts that the "polymorphism and haplotype data disclosed herein are useful for studying population diversity, anthropological lineage, the significance of diversity and lineage at the phenotypic level, paternity testing, forensic applications, and for identifying associations between the IL4Rα genetic variation and a trait such as level of drug response or susceptibility of disease." These utilities are not particularly asserted as utilities for the claimed invention (as they are asserted utilities for data, not a method), nonetheless it is noted that these utilities are neither specific nor substantial with regard to the claimed invention. They are not specific to the claimed invention because they could be applied to any set of genetic markers in any gene for the partitioning of human populations. They are not substantial because they are an invitation to do further research

in order to determine if the haplotype pairs disclosed herein are actually useful for any particular method.

Once one has carried out the method of the claimed invention and "assigned a haplotype pair to an individual that is consistent with the data," one has essentially assigned an arbitrary identifier to the gene of an individual. There is no particular relevance disclosed in the specification for any particular predicted haplotype pair. The prediction method herein is a method which results in the assignment of a haplotype pair to an individual simply for no end other than to make the assignment. Furthermore, it is noted that the methods are drawn to "predicting" a haplotype pair, and do not necessarily assign an accurate haplotype pair to an individual, but instead result in the assignment of a haplotype pair that is "consistent with the data" in table 4. The data in table 4 themselves are not empirical data but are an estimation of possible haplotype pairs in a population, and thus the assignment of a predicted haplotype pair based on that data is another step away from an actual empirical determination of the haplotype pair present in an individual's genome. Furthermore, the data in table 4 are not complete, leaving the identity of a polymorphism present in some polymorphic sites blank to be inferred by "mendelian genetics or linkage disequlibrium." Thus, on another level, since the method is actually one more of "estimation" of a haplotype pair present in an individual than a method of actually determining that any particular haplotype pair is present in the genome of an individual, it is further clear that there is no specific or substantial utility for the arbitrary assignment of a haplotype pair label for an individual.

Claims 26-30 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well

established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The breadth of the claims and the teachings provided in the specification with regard to the asserted utilities of the instant invention are previously discussed in the rejection under 35 U.S.C. 101. The specification does not provide a single working example wherein the instant method is used in any real world context, but instead only postulates that the haplotype data in the specification may be useful in a variety of methods directed at determining if in fact the disclosed haplotypes are associated with any biological phenotype or phenomena of interest. Essentially, the haplotype prediction of the claimed method is a method wherein a putative haplotpye pair is predicted for an individual based on two layers of estimations and assumptions. The first layer is the layer wherein the haplotype pairs of table 4 themselves were derived using a convolution analysis, that is, the haplotype pairs were not empirically observed, but were statistically predicted. The second layer is the prediction itself, which is also based on an analysis of predicted haplotype pairs in a sample. In order to reasonably confirm the validity of the haplotype prediction method, a large quantity of experimentation would be required by the skilled artisan, for example, the direct sequencing of hundreds of copies of the IL4Rα from different individuals to actually empirically determine the haplotype pairs present in a population. Furthermore, even after the validity of the methods of predicting the haplotype pair were confirmed, one skilled in the art still would have only a method for assigning an arbitrary identifier to an individual's IL4Rα gene copies. One still would not know the relevance of the fact that a particular individual has a "1, 2" haplotype pair. To determine how to use this invention would require experimentation which would result in determining some relevance of

the actual haplotype assignment. Such experimentation in itself would be inventive, and thus the claims are also rejected under 112 1st paragraph for lack of provision of an enabling use for the claimed invention.

Even if applicant were to overcome the previous rejections and establish a patentable utility for the claimed invention, claims 26-29 would be further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for predicting a haplotype pair for the IL4Rα gene wherein the identifying step of part (a) utilizes methodologies wherein each of the polymorphic sites are directly genotyped, does not reasonably provide enablement for method wherein the identifying step comprises indirectly determining the genotype of the polymorphic sites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Breadth of the Claims**

The rejected claims are drawn to a method of predicting a haplotype pair for the interleukin 4 receptor alpha (IL4Rα) of an individual and comprise a first step of "identifying the IL4Rα genotype for the individual" at each of thirty-nine different polymorphic sites. The specification teaches that such genotyping can occur via direct methods of direct detection of polymorphic sites, including for example, primer extension assays, an allele-specific PCR, a nucleic acid amplification assay, a sequencing assay, etc.. The specification also asserts that a the identity of an allele present at a polymorphic site can be "indirectly determined by genotyping a polymorphic site not disclosed herein that it is linkage disequilibrium with the polymorphic site that is of interest (p. 49)," and specifically recited in claim 29. Each of the

claims rejected herein encompass methods wherein the identification of polymorphic sites occurs by such indirect determination.

**Guidance in the specification and Working Examples**

The specification teaches a set of polymorphic sites within the IL4Rα gene that were identified by sequencing portions of the IL4Rα from two reference populations (referred to in the examples as Index Repository IA (example 1a) and another population of 70 human individuals (example 1b). The positions of the polymorphic sites within a reference sequence are given in Table 3, and illustrated in Figure 1. In example 2, Table 4, the specification provides a sampling of different genotypes containing the polymorphisms that were observed in the reference population, specifically teaching haplotype pairs that were determined using a "derivation protocol." Table 4 contains a listing of haplotype pairs observed in the reference populations for 39 polymorphic sites, but Table 4 also contains some blanks where particular alleles are not identified. The specification teaches that these can typically "be inferred based on linkage disequilibrium and/or Mendelian inheritance." Example 2 teaches that the haplotype pairs were estimated from the unphased genotypes using an extension of Clark's algorithm. Thus, the haplotype pairs presented in Table 4 are not themselves empirically observed haplotype pairs but are an estimation that were deconvulated based on unphased genotypes.

The specification does not, however provide any further guidance as to how to accomplish the identification of a genotype by indirect methodology based on linkage disequilibrium and/or Mendelian inheritance. In particular, the specification does not identify which of the disclosed polymorphisms are in linkage disequilibrium with one another such that the identity of one can reliably be used to predict the identity of another, and further, the

specification does not provide any guidance as to any polymorphisms outside of those identified as particular polymorphic sites in the specification that might be in linkage disequilibrium with the recited polymorphic sites. While the description clearly discloses that the identity of a nucleotide may be "determined" by examining a subset of polymorphic sites and inferring the identity of other polymorphic sites, the description never discloses which polymorphic site or sites must be examined in order for a skilled artisan to draw conclusions concerning the identity of other polymorphic sites.

The specification does not provide a working example wherein a genotype is identified using inferred identification of a polymorphic site either based on the identity of a polymorphic site disclosed herein or a polymorphic site not disclosed herein.

**Guidance in the Prior Art**

Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for enablement of a claimed invention. The prior art as exemplified by Deichmann *et al.* (Biochemical and Biophysical Research Communications, 231, 696-697, 1997) discloses the detection and sequencing of the IL4Rα gene, and further disclose common polymorphisms within the coding region of the gene. However, the prior art does not disclose what particular polymorphism or combinations of polymorphism must be detected in order for one to reach a conclusion infer the identity of a remaining set of polymorphisms within an individual's genome. Accordingly, neither the description nor the art provide guidance with respect to which subsets of polymorphic sites must be examined to practice methods in which a genotypes at particular polymorphic sites is "identified" by examining a subset of polymorphic sites and making inferences to determine the remaining polymorphisms. Further, no guidance is

provided as to which polymorphic sites outside of those identified herein as PS1-PS45 might possible be in linkage disequlibirum with any of the instantly disclosed polymorphic sites. Lacking this critical information, no quantity of experimentation would be sufficient to practice such methods of identifying an IL4Rα genotype for an individual at the 39 recited polymorphic sites using indirect means.

**Level of Unpredictability and Quantity of Experimentation**

Absent the undertaking of extensive experimentation and screening to determine which polymorphic sites are sufficiently predictive of one another within the set of 45 taught in the specification, and extensive screening of the regions of the genome surrounding the IL4Rα gene to determine additional polymorphic sites that are in linkage disequlibirium with the recited polymorphic sites, the practice of the claimed invention with regard to indirect determination and therefore the specification does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed step of "identifying an IL4Rα genotype" to be carried out by a person skilled in the art in a manner commensurate with the claims. Though the level of skill in the art is quite high, there is a higher level of unpredictability with regard to which polymorphic sites can be used as predictors of the identity of neighboring sites, and outside of the 45 polymorphic sites taught in the specification it is entirely unpredictable as to which of the polymorphic sites that are "not disclosed herein" but may be useful in the instant methods for predicting haplotype pairs.

**Conclusion**

Thus, in light of the breadth of the claims, the lack of working examples in the specification, the lack of guidance in the prior art, the high level of unpredictability in the art and

the high quantity of experimentation required, it is concluded that undue experimentation would be to practice the claimed invention commensurate in scope with the instant claims, even if all concerns regarding the utility of the claimed invention were overcome.

**Response to Remarks**

Applicant argues that the specification asserts that methods for establishing the IL4Rα haplotpye of an individual are useful for "predicting individual susceptibility to diseases affected by the expression and function of the IL4Rα protein (p. 5 of response)." However, this is not a complete representation of what the specification asserts. The specification asserts that "establishing the genotype or haplotype of an individual at the ***novel*** polymorphic sites herein are useful for...predicting individual susceptibility to diseases affected by the expression and function of the IL4Rα protein (p. 7 of specification, lines 18-22; emphasis added)." Applicant's arguments presented in the response, however, focus on a utility of determining the identity of the polymorphic sites within the haplotypes that are not novel, but instead that were known in the prior art at the time the invention was made. The utility asserted in the instant specification concerns the novel polymorphisms of the instant invention, not polymorphisms that were known in the art at the time the invention was made. Furthermore, the associations between IL4Rα polymorphisms and disease are not well settled in the prior art, and are indeed highly unpredictable. For example, Hackstein *et al.* (as cited in IDS) tested 158 blood donors and did not find a relationship between IL4Rα polymorphisms and atopy (see at least abstract), while Ober *et al.* observed a relationship between some IL4Rα polymorphisms and atopy or asthma, but the alleles conferring susceptibility differed between populations. Even if one could impute

a disease predisposition utility on the claimed invention based on previous knowledge in the prior art, the claims would not be enabled for their full scope because there is not sufficient enablement in the specification or the prior art for the detection of any and all possible diseases that are "affected by the expression and function of the IL4Rα protein." Furthermore, the claimed invention is not for a method of predicting the presence or predisposition to disease, it is to a method of predicting a haplotype, that is the set of alleles present in a collection of polymorphic sites.

Applicant further argues that the haplotyping methods are useful for "studying the efficacy of drugs targeting IL4Rα (p. 5 of response)," however no evidence is provided that the instant haplotypes are in any way related to a particular drug or drugs that target IL4Rα. This statement of a utility is an invitation to conduct further research to determine if a real world utility for the claimed invention actually exists, and is not a substantial utility. To support this assertion of a utility, applicant cites a general teaching in a WO publication of methods of using polymorphism data to segregate populations. While generically such methods may have utility, absent a showing in the specification that this type of methodology is applicable to the instantly disclosed methodologies, and that a useful result is obtained, such a utility is not a substantial utility for the claimed invention. Again, it is an invitation to see if a substantial utility exists.

It is acknowledged that deconvolution as a methodology for determining haplotypes based on a dataset was a routinely used methodology at the time the invention was made. Nonetheless, it remains that the specification is not enabling for methods of predicting haplotype pairs using "indirect determination" of polymorphic sites based on, for example, linkage between the disclosed polymorphic sites or, and perhaps especially, linkage to polymorphisms that are

"located in regions of the gene or in other genomic regions not examined by Applicants (as discussed in the response p. 9)." Though methods for establishing linkage between two polymorphic sites were known at the time the invention was made, this does not mitigate the fact that there is no clear guidance given in the specification as to which of the disclosed polymorphic sites are sufficiently linked to be reliably predictive of one another, and even more, which undisclosed polymorphisms on chromosome 16 or within other portions of the IL4Rα gene are so linked. Linkage between two sites is highly unpredictable, as noted by applicant, a review of table 4 suggests that perhaps PS 42 and PS45 are linked to one another but not to intervening PS 44. However, the confirmation of even these relationships would require further, unpredictable experimentation on the part of the skilled artisan. Applicant further asserts that because general methodology for screening for polymorphisms was well known at the time the invention was filed, the identification of additional polymorphic sites that might be in linkage disequilibirum with the disclosed sites would not require undue experimentation. However, the knowledge of a general methodology such as how to screen for polymorphic sites does not overcome the fact that the identity of these additional sites, and indeed, whether or not they even exist and are in linkage with the claimed invention is highly unpredictable. The specification does not give any guidance as to the identity of these sites or which polymorphisms within the disclosed haplotypes they might be in association with. Thus, for the reasons of record, the rejection is maintained.

***Conclusion***

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

January 16, 2004

W. GARY JONES
SUPERVISORY PATENT EXAMINER
TC 1600